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| 09/103,745 | 06/24/1998 | SUDHIR AGRAWAL | IDRA-740US1 | 3401 |

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Preti Flaherty
PO Box 9546
One City Center
Portland, ME 04112-9546

| EXAMINER | |
|---|---|
| WOLLENBERGER, LOUIS V | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 07/01/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

wkeown@preti.com
jczucchero@woodphillips.com
info@woodphillips.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/103,745 | AGRAWAL, SUDHIR | |
| | Examiner | Art Unit | |
| | Louis Wollenberger | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of the method of claims 16-19 wherein the "gene or RNA transcript is from edogenous mammalian chromosomal DNA" in the reply filed on 5/14/2010 is acknowledged. Applicant is advised this is an election of species not an invention.

The traversal is on the ground(s) that the invention is independent of the sequence of the gene or RNA transcript to which the oligo is complementary. This is not found persuasive because the claims as now written, nevertheless, require a search and consideration of the target gene as a part of the consideration of the patentability of the claimed method as a whole. Searching multiple different target genes or classes of genes in each action on the merits presents a serious burden.

The requirement is still deemed proper and is therefore made FINAL.

### *Status of Application/Amendment/Claims*

Applicant's response filed 2/24/2010 to the Final Rejection mailed 12/24/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/24/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Also acknowledged are Applicant's amendments to the claims filed 2/24/2010 and 5/14/2010. The amendments have been entered into the application. With entry of the amendment filed 5/14/2010, claims 16-19 are pending and examined herein.

***Claim Rejections - 35 USC § 112, first paragraph (new matter)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Upon careful reconsideration, Claims 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Adequate written description support is not found in the instant application for the genus modified CpG-containing phosphorothioate oligonucleotides wherein the C and/or G of each CpG dinucleotide "and only the CpG dinucleotide" present in the oligonucleotide is modified with a 2'-O-methyl. Consequently, written description support is not found for the genus of methods of administering or otherwise using said modified oligonucleotides. Rather, a review of the application as filed finds description for phosphorothioate oligonucleotides having "one or more modified CpG dinucleoside." See page 7, lines 36-37. The specification further teaches that in certain preferred embodiments "all CpG dinucleosides present in the oligonucleotide are modified." See page 8, lines 7-9. Disclosure beginning at page 13, line 21, further teaches the inventor contemplates hybrid and chimeric oligos, where, in addition to the modified CpG, 2'-O-substituted ribonucleotide regions include from "one to all nonionic internucleoside linkages." See page 13, line 35-37. Moreover, the working examples do not particularly describe or show

the oligonucleotide sequences and modifications used therein in a manner that might provide implicit support for the limitation now recited by the claims. There is certainly no language in the application as filed expressly identifying or particularly recognizing those embodiments wherein the CpG *and only the CpGs* are modified. On the contrary the application teaches that the modification of CpGs may be included with other 2'-sugar modified residues, as in the hybrid or chimeric configurations known in the prior art. The application teaches that it is the modification of the C and/or G in CpGs that is essential to the reduction of immunostimulatory activity of an oligonucleotide, but does not each that the modification should or, optionally, may be carried out to the exclusion of other nucleotides.

Accordingly, the Examiner fails to find explicit or even implicit support for the limitation in the claims wherein "only the CpG dinucleotide[s]" present the oligonucleotide are modified with 2'-O-methyl. While the application teaches that one or more and in some cases all of the CpGs should be modified, the application does not teach that one should avoid modifying all other nucleotides with 2'-O-methyl as part of the invention and there are no exemplary embodiments found that might be representative of the limitation.

The Examiner notes that in the Remarks filed 9/8/2009, when the limitation was initially introduced into the claims, Applicant had pointed to disclosure at pages 7 and 8 as support for the amendment. However, the disclosure here does not reasonably represent or describe the exclusionary requirement now recited by the claims.

MPEP 2163, Section II, Part A, states in part that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended

claims, applicant should show support in the original disclosure for the new or amended claims. The purpose of the written description requirement is "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." MPEP 2138.05, I.

Accordingly, the instant claims as a whole are rejected for lack of written description support because one of skill would not recognize applicant was in possession of the methods now claimed at the time of filing. Should Applicant disagree with the finding, Applicant is invited to point out with particularity where and how written description support may be found in the original application.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matulic-Adamic et al. (US Patent 5,998,203), Zhang et al. (1995) *Biochemical Pharmacology* 50:545-556, and Temsamani et al. (1992) Antisense Strategies "Capped oligodeoxynucleotide phosphorthioates: Pharmocokinetics and stability in mice" *Annals of New York Academy of Sciences*, pp. 318-320, the combination in view of Bennett et al. (US 5843738).

The claims are drawn to providing and administering CpG-containing phosphorothioate oligonucleotides, wherein the C and/or G of each CpG dinucleotide, and only the CpG dinucleotide, present in the oligonucleotide is modified with a 2'-O-methyl. The specification at page 7, line 37, to page 8, line 1, teaches that the CpG dinucleotide "is 5'-CpG-3', i.e., in the 5' to 3' direction,..." The claims clearly embrace this embodiment.

The prior art had taught that deoxy- and ribonucleic acids designed for inhibition of gene expression are more stable in vivo when they are chemically modified at the 5' and/or 3' ends.

For example, Matulic-Adamic et al. had taught the addition of a 5' and/or 3' end cap structure to DNAzymes and ribozymes (nucleic acids that cleave complementary DNA and RNA targets) protects the nucleic acids from exonuclease degradation and generally improves their stability in nuclease-rich environments. In one embodiment, the 3' and 5' cap is a 2'-O-methyl modified nucleotide (cols. 1-7; col. 3, lines 4-30 and bridging to col. 4; see definition of "alkyl" at column 5).

Zhang et al., in a report about the in vivo stability of antisense oligonucleotides, had taught that phosphorothioate oligonucleotides are metabolized in various tissues primarily by 3'-exonucleases, and that degradation of PS-oligonucleotides in vivo reduces their effectiveness for

longer duration. It is said that, therefore, stabilization of PS-oligonucleotides to avoid degradation in vivo may improve their effectiveness. Zhang et al. showed that the stability of a phosphorothioate antisense oligonucleotide could be further improved by incorporation of 2'-O-methyl modified nucleotides at the 3' and 5' ends of the molecule

Temsamani et al. showed that, in mice, degradation of oligonucleotide phosphorothioates occurs mainly by 3' exonuclease activity, and that this degradation can be slowed down by appropriate modification at the 3' end of the oligonucleotide.

Accordingly, the prior art had suggested chemically modifying the 3' and/or 5' terminal riboses in antisense phosphorothioates at the 2' position to improve stability in vivo. The prior art, cited above, teaches that the chemical modification may be a 2'-O-methyl.

It would therefore have been prima facie obvious at the time of invention to one of ordinary skill in the art to chemically modify the 5' and/or 3' terminal ribose of any known nucleic acid therapeutic, including any known antisense phosphorothioate, to improve the stability of the oligonucleotide in nuclease-rich environments such as those encountered in vivo. At the time of invention, Zhang et al. had shown that the stability of a phosphorothioate antisense oligonucleotide could indeed be further improved by incorporation of 2'-O-methyl modified nucleotides at both ends of the molecule. In view of Matulic-Adamic et al., one of skill might reasonably have known that 2'-O-methyl modification of either end would lead to improvement. See for example, results at working example 4, col. 24, describing the effect of 5'-end modifications. Temsamani et al. had taught that the addition of a single chemical modification at the 3' end of a phosphorothioate antisense oligonucleotide can significantly improve the durability of the oligonucleotide in the presence of exonucleases.

Bennett et al. had taught a number of phosphorothioate antisense oligonucleotides for inhibiting the expression of human VCAM-1 (Table 4, cols. 23-24). The oligonucleotide inhibitors are said to be useful for the treatment of inflammatory diseases, diseases with an inflammatory component, allograft rejection, psoriasis and other skin diseases, inflammatory bowel disease, cancers and their metastasis, and viral infections (see Summary of the Invention, col. 6), where the expression of VCAM-1 may contribute to the inflammatory response. PS-oligonucleotides identified and preferred by Bennett et al. for inhibiting VCAM-1 include the 20-nucleotide sequence defined by SEQ ID NO:63 (see sequences noted with asterisk in Table 4). As is clear from the nucleotide sequence, SEQ ID NO:63 has a single CpG on the 3' end. Therefore, one of skill following the practice in the prior art teaching that the PS-oligonucleotides may be further stabilized by adding a chemical group such as a 2'-O-methyl to the 3'-terminal ribose with any of the VCAM-1 antisense PS-oligonucleotides disclosed by Bennett et al. in Table 4 would, in the case of SEQ ID NO:63, produce and inevitably provide a 20-nucleotide CpG-containing PS-oligonucleotide wherein the G of each CpG dinucleotide and only the CpG present in the oligonucleotide is modified with a 2'-O-methyl. All biological effects intrinsically associated with such a molecule, including those recited by the instant claims, would necessarily flow from the use of such molecule (MPEP 2112).

Accordingly, the prior art had suggested a method within the scope of the instant claims.

***Prior art made of record but not currently relied on***

The following prior art is made of record and is not currently relied upon, but is considered pertinent to applicant's disclosure.

Robert et al. (US 2001/0010899 A1):

Citing from US Provisional Application 60/021,041, Robert et al. taught CpG-containing phosphorothioate antisense oligonucleotides for inhibiting human papilloma viral gene expression in an infected host cell in a human (pp. 1-58; Tables 1A and B). Means and modes of administration to an individual of any of the antisense oligos are disclosed (page 1-58). In certain embodiments the anti-HPV oligonucleotides comprise a single CpG at the 3' end of the molecule. See for example the oligos referred to therein as HPV6 and HPV36, Table 1A, page 17. Robert et al. further explicitly and implicitly disclosed the phosphorothioate antisense oligonucleotides may be capped at their 3' and/or 5' ends with a nuclease resistance-conferring bulky substituent (page 14, beginning at line 29; see also disclosure at pages 11-14). Examples of such substituents are said to include a 2'-O-methyl, as shown in Table 1B (page 14, lines 29-38).

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
June 23, 2010